UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,011	06/20/2003	Ciaran N. Cronin	SYR-AIK-5001-C1	5098

32793 7590 06/12/2007

TAKEDA SAN DIEGO, INC.
10410 SCIENCE CENTER DRIVE
SAN DIEGO, CA 92121

EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
06/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/601,011	CRONIN ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,9,12,15,17,18,22-25 and 27-33* is/are pending in the application.

4a) Of the above claim(s) *18 and 22-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,9,12,15,17 and 27-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendix A*.

DETAILED ACTION

Status of the Application

[1] Claims 1, 4, 9, 12, 15, 17-18, 22-25, and 27-33 are pending in the application.

[2] Applicant's amendment to the claims, filed on 3/22/07, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's amendment to the specification, filed on 3/22/07, is acknowledged.

[4] Applicant's arguments filed on 3/22/07, in response to the Office action mailed on 9/22/06 have been fully considered and are deemed to be persuasive to overcome the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

[6] Claims 18 and 22-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/31/06.

Specification/Informalities

[7] The specification is objected to as being inconsistent as identifying the amino acid sequence of the atomic coordinate listing of Figure 3 as SEQ ID NO:1. According

to Figure 3, the first amino acid in the listing is Ala. However, the paper copy of the sequence listing identifies Met as the first amino acid of SEQ ID NO:1. Appropriate correction is required.

Claim Rejections - 35 USC § 101

[8] In view of the amendment to claim 30 to recite "A protein consisting of...", the rejection of claim 30 under 35 U.S.C. 101 is withdrawn. According to the specification, residues 125-391 of SEQ ID NO:1 are the kinase domain of wild-type AIK (p. 13, paragraph 53). In this case, there is no evidence of record that the SEQ ID NO:1 fragment of residues 125-391 occurs in nature and rather requires the hand of man to produce this polypeptide fragment.

Claim Rejections - 35 USC § 112, First Paragraph

[9] Claims 31-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

According to applicant, amino acids 1-31 of SEQ ID NO:3 are a His tag, a first spacer, a TEV cleavage site, and a second spacer (instant remarks at p. 6, middle). Applicant notes that the polypeptide as recited in claims 31-33 is an rTEV cleavage product of SEQ ID NO:3, the specification discloses rTEV cleavage of SEQ ID NO:3 at

paragraph 195, and it is well-known in the art that rTEV cleaves between a Gln-Gly junction, and thus a skilled artisan would recognize that applicant was in possession of the recited polypeptide having the range of amino acids 24-295 of SEQ ID NO:3.

It is noted that there is no evidence of record to support applicant's allegation that rTEV cleaves at a Gln-Gly junction. The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). It is further noted that Figure 1 of the drawing figures would appear to contradict applicant's assertion. According to Figure 1, bottom (relevant portion reproduced below for applicant's convenience), it is shown that the N-terminal portion up to an amino acid corresponding to amino acid 125 of SEQ ID NO:1 is cited as being the cleavage site. As such, the introduction of this range of amino acids into the claims is considered to be new matter. It is suggested that applicant show support for the limitation at issue.

Amino acid sequence for residues 125-391 of AIK with a cleavable (rTev) N-terminal 6x-histidine tag [SEQ. ID No. 3] (6x-histidine tag and cleavage site are underlined)

MSYYHHHHHH DYDIPTTENL YFQGAMGSKR QWALEDFEIG RPLGKGKFGN VYLAREKQSK	60
FILALKVLFK AQLEKAGVEH QLRREVEIQS HLRHPNILRL YGYFHDATRV YLILEYAPLG	120
TVYRELQKLS KFDEQRTATY ITELANALSY CHSKRVIHRD IKPENLLLGS AGELKIADFG	180
WSVHAPSSRR TTLCGTLDYL PPEMIEGRMH DEKVDLWSLG VLCYEFLVGK PPFEANTYQE	240
TYKRISRVEF TFPDFVTEGA RDLISRLLKH NPSQRPMLRE VLEHPWITAN SSKPS	295

[10] The written description rejection of claim(s) 1, 4, 9, 12, 15, 17, and 27-30 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action. Newly added claims 31-33 are included in the instant rejection for reasons that follow. Thus, claims 1, 4, 9, 12, 15, 17, and 27-33 are rejected.

RESPONSE TO ARGUMENT: Regarding claims 1 and 9, applicant argues the rejection is obviated by claim amendment to recite space group and unit cell dimensions.

Applicant's argument is not found persuasive. The examiner maintains the position that the specification fails to adequately describe the genus of compositions and crystals as encompassed by the claims. The examiner acknowledges the amendment to claims 1 and 9 to limit the claims to recitation of the sequence of the protein, the space group, and unit cell dimensions of the crystal. However, the examiner maintains the position that the specification fails to describe all crystallized proteins as encompassed by the claims. Claim 1 is drawn to a composition comprising a protein in crystalline form with the recited space group and unit cell dimensions. In view of the transitional phrase "comprising," the examiner has interpreted the composition as a crystal of residues 125-391 of SEQ ID NO:1, optionally with *any other ligand(s).* Put another way, the genus of compositions and crystals includes crystals of residues 125-391 of SEQ ID NO:1 in its native form, *i.e.,* unliganded, and crystals of residues 125-391 of SEQ ID NO:1 with any ligand(s) bound thereto. Thus, the genus of compositions and crystals encompasses widely variant species. However, as noted in the prior Office action, the specification discloses only a single disclosed species of crystals, *i.e.,* a crystal of residues 125-391 of SEQ ID NO:1 in complex with ATPγS having the space group symmetry $P6_122$ and having vector lengths a=b=80.45 Å, and c=172.18 Å (p. 24, Table 6), which diffracts X-rays to a resolution of 1.9 Å (specification at pp. 24-25, Table 6), and only a single method for its crystallization, *i.e.,* the method disclosed at p. 48, ¶¶

[00198] and [0199] of the specification. Thus, as noted in the prior Office action, the genus of compositions and crystals encompass species that are widely variant, including species of unliganded and liganded forms of residues 125-391 of SEQ ID NO:1, wherein the liganded form is in complex with *any* ligand and methods of making therefor. It should be noted that the specification fails to disclose even a single representative species of compositions, crystals, and methods as encompassed by claims 31-33. As evidenced by the amino acid sequence alignment of Appendix A, residues 24-295 of SEQ ID NO:3 have an N-terminal extension relative to residues 125-391 of SEQ ID NO:1 and as noted in the prior Office action, there is no way to predict *a priori* the space group and unit cell dimensions of a protein, as evidenced by the references of Kierzek et al. (cited in a prior Office action; see cited relevant teachings). As such, even though the disclosed crystal is of a polypeptide that shares a substantial structural feature with the polypeptide of residues 24-295 of SEQ ID NO:3, there is no way to predict whether such a crystal of residues 24-295 of SEQ ID NO:3 would crystallize under the same conditions to achieve a crystal having the identical space group and unit cell dimensions.

Other than the single species as noted above, the specification fails to describe any other compositions or crystals or methods for crystallization thereof as encompassed by the claims. MPEP § 2163 states "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." As such, the single disclosed species of compositions and crystals and methods for making said

crystal as noted above fail to adequately describe all compositions, crystals, and methods as encompassed by the claims. Given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

Regarding claims 17 and 30, applicant argues the specification adequately describes the claimed protein, referring to Example 13 of the Written Description Guidelines.

Applicant's argument is not found persuasive. MPEP § 2111.01 states, "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." While it is acknowledged the claims are drawn to "[a] protein...", claims 17, 30, and 31 have been broadly, but reasonably interpreted as encompassing a protein in a crystalline form, particularly as the disclosure of the specification is directed to protein crystals. "[T]he specification 'is always highly relevant to the claim construction analysis. Usually it is dispositive; it is the best single guide to the meaning of a disputed term.'" *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315, 75 USPQ2d 1321, 1327 (Fed. Cir. 2005).

For reasons discussed above, the single disclosed representative species of protein crystals fails to reflect the structural variation among the members of the genus. As noted in the prior Office action, there is no way to predict *a priori* the space group and unit cell dimensions of a protein, as evidenced by the references of Kierzek et al. (cited in a prior Office action; see cited relevant teachings) and Buts et al. (*Acta Crystallogr. D.*, vol. 61, pages 1149-1159, 2005; cited in a prior Office action), which

teaches that even a single amino acid mutation can alter the space group symmetry and unit cell dimensions of a crystallized protein. As noted in the prior Office action, it is well-known in the art that a single polypeptide can have a plurality of distinct crystal forms, which one cannot predict *a priori* (see, *e.g.,* Aleshin et al. *FEBS Lett* 434:42-46, 1998; cited in a prior Office action).

At least for the reasons of record and reasons stated herein, the specification fails to adequately describe the claimed invention.

[11] The scope of enablement rejection of claim(s) 1, 4, 9, 12, 15, 17, and 27-30 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action. Newly added claims 31-33 are included in the instant rejection for reasons that follow. Thus, claims 1, 4, 9, 12, 15, 17, and 27-33 are rejected.

RESPONSE TO ARGUMENT: Applicant argues the specification enables the full scope of the claimed invention, particularly as the specification discloses working examples and how to make variants.

Applicant's argument is not found persuasive. The examiner maintains the position that the specification, while being enabling for a crystal of residues 125-391 of SEQ ID NO:1 in complex with ATPγS having the space group symmetry $P6_122$ and having vector lengths a=b=80.45 Å, and c=172.18 Å (p. 24, Table 6), which diffracts X-rays to a resolution of 1.9 Å (specification at pp. 24-25, Table 6), a method for its crystallization, *i.e.,* the method disclosed at p. 48, ¶¶ [00198] and [0199] of the

specification, and measuring serine-threonine kinase activity, does not reasonably provide enablement for all compositions, crystals, methods of crystallization, and measured activities as broadly encompassed by the claims.

The breadth of the claims: The claims are so broad as to encompass: crystals of residues 125-391 of SEQ ID NO:1 or residues 24-295 of SEQ ID NO:3 that are unliganded or have any bound ligand, essentially any method of crystallization thereof, and a method of measuring any "activity" of the protein. Also, as noted above, claims 17, 30, and 31 have been broadly, but reasonably interpreted as encompassing a protein consisting of SEQ ID NO:3, a protein consisting of residues 125-391 of SEQ ID NO:1, and a protein consisting of residues 24-295 of SEQ ID NO:3 in crystalline form. The broad scope of the claims is not commensurate with the enablement provided by the disclosure. In this case the disclosure is limited to a crystal of residues 125-391 of SEQ ID NO:1 in complex with ATPγS having the space group symmetry $P6_122$ and having vector lengths a=b=80.45 Å, and c=172.18 Å (p. 24, Table 6), which diffracts X-rays to a resolution of 1.9 Å (specification at pp. 24-25, Table 6), a method for its crystallization (p. 48, ¶¶ [00198] and [0199] of the specification) and a single measurable activity, *i.e.,* serine-threonine kinase activity.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The state of the art at the time of the invention acknowledges a **high** level of unpredictability for making a protein crystal with an expectation that it is diffraction-quality. Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999; cited in a prior Office action) teaches that "[c]rystallization

is usually quite difficult to achieve" (p. 375) and that "[w]ell-ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth ("Principles of X-ray Crystallography," Springer, New York, 1995; cited in a prior Office action) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al. (*Biophys Chem* 91:1-20, 2001; cited in a prior Office action), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). Thus, in view of these teachings, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of other AIK polypeptides optionally having a desired space group and unit cell dimensions as encompassed by the claims can be achieved using *any* crystallization parameters. Even assuming *arguendo* one can achieve diffraction-quality crystals, it is noted that Branden et al. teaches that only a few small proteins have been determined to a resolution of 1 Angstrom (p. 382, middle).

The amount of direction provided by the inventor; The existence of working examples: The specification discloses the utility of the claimed crystal is in the determination of the

3-D structure of Aurora kinase and the design of small molecule inhibitors (p. 2, paragraphs [0006] and [0007]), which, as acknowledged by Branden et al. (*supra*) at p. 374, requires a diffraction-quality crystal. In this case, the specification discloses only a single working example of such a diffraction quality crystal, *i.e.,* a crystal of residues 125-391 of SEQ ID NO:1 in complex with ATPγS having the space group symmetry $P6_122$ and having vector lengths a=b=80.45 Å, and c=172.18 Å (p. 24, Table 6), which diffracts X-rays to a resolution of 1.9 Å (specification at pp. 24-25, Table 6); the specification discloses only a single working example of a method for successfully crystallizing residues 125-391 of SEQ ID NO:1, *i.e.,* crystallization method at p. 48, ¶¶ [00198] and [0199] of the specification; and discloses only a single working example of activities of the protein that can be measured, *i.e.,* serine-threonine kinase activity. Other than these working examples, the specification fails to provide guidance regarding crystals, methods for crystallization, and other measurable activities as encompassed by the claims. It should be particularly noted that the specification fails to disclose even a single working example of a crystal of residues 24-295 of SEQ ID NO:3 or a method of crystallization thereof.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of protein crystallography were known at the time of the invention, it was not routine in the art to make all compositions and crystals as encompassed by the claims for those that will yield diffraction-quality crystals using any crystallization conditions as encompassed by the claims.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use all crystals and polypeptides as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

[12] The rejection of claim 30 under 35 U.S.C. 102(b) as being anticipated by Plowman et al. (US Patent 5,962,312) is withdrawn in view of the claim amendment to limit the protein to "consisting of residues 125-391 of SEQ ID NO:1." While Plowman et al. teaches the Aur-2 kinase domain is "preceded by a N-terminal domain of...130 amino acids" (column 29, lines 8-10), Plowman et al. does not appear to teach or suggest a protein consisting of residues 125-391 of SEQ ID NO:1.

Conclusion

[13] Status of the claims:

- Claims 1, 4, 9, 12, 15, 17-18, 22-25, and 27-33 are pending.
- Claims 18 and 22-25 are withdrawn from further consideration.
- Claims 1, 4, 9, 12, 15, 17, and 27-33 are rejected.
- No claim is in condition for allowance.

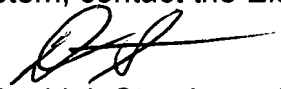
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656

APPENDIX A

Query sequence 1

>125-391 SEQ ID NO:1
KRQWALEDFEIGRPLGKGKFGNVYLAREKQSKFILALKVLFKAQLEKAGVEHQLRREVEI
QSHLRHPNILRLYGYFHDATRVYLILEYAPLGTVYRELQKLSKFDEQRTATYITELANAL
SYCHSKRVIHRDIKPENLLLGSAGELKIADFGWSVHAPSSRRTTLCGTLDYLPPEMIEGR
MHDEKVDLWSLGVLCYEFLVGKPPFEANTYQETYKRISRVEFTFPDFVTEGARDLISRLL
KHNPSQRPMLREVLEHPWITANSSKPS

Query sequence 2

>24-295 of SEQ ID NO:3
GAMGSKRQWALEDFEIGRPLGKGKFGNVYLAREKQSKFILALKVLFKAQLEKAGVEHQLR
REVEIQSHLRHPNILRLYGYFHDATRVYLILEYAPLGTVYRELQKLSKFDEQRTATYITE
LANALSYCHSKRVIHRDIKPENLLLGSAGELKIADFGWSVHAPSSRRTTLCGTLDYLPPE
MIEGRMHDEKVDLWSLGVLCYEFLVGKPPFEANTYQETYKRISRVEFTFPDFVTEGARDL
ISRLLKHNPSQRPMLREVLEHPWITANSSKPS

Full-length alignment between two sequences

>>24-295 of SEQ ID NO:3 (272 aa)
s-w opt: 1787 Z-score: 2195.4 bits: 414.0 E(): 1.8e-120
Smith-Waterman score: 1787; 100.000% identity (100.000% ungapped) in 267 aa overlap (1-267:6-272)

```
                    10        20        30        40        50
125-39       KRQWALEDFEIGRPLGKGKFGNVYLAREKQSKFILALKVLFKAQLEKAGVEHQLR
             ::::::::::::::::::::::::::::::::::::::::::::::::::::::
24-295 GAMGSKRQWALEDFEIGRPLGKGKFGNVYLAREKQSKFILALKVLFKAQLEKAGVEHQLR
               10        20        30        40        50        60

           60        70        80        90       100       110
125-39 REVEIQSHLRHPNILRLYGYFHDATRVYLILEYAPLGTVYRELQKLSKFDEQRTATYITE
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
24-295 REVEIQSHLRHPNILRLYGYFHDATRVYLILEYAPLGTVYRELQKLSKFDEQRTATYITE
               70        80        90       100       110       120

         120       130       140       150       160       170
125-39 LANALSYCHSKRVIHRDIKPENLLLGSAGELKIADFGWSVHAPSSRRTTLCGTLDYLPPE
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
24-295 LANALSYCHSKRVIHRDIKPENLLLGSAGELKIADFGWSVHAPSSRRTTLCGTLDYLPPE
              130       140       150       160       170       180

         180       190       200       210       220       230
125-39 MIEGRMHDEKVDLWSLGVLCYEFLVGKPPFEANTYQETYKRISRVEFTFPDFVTEGARDL
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
24-295 MIEGRMHDEKVDLWSLGVLCYEFLVGKPPFEANTYQETYKRISRVEFTFPDFVTEGARDL
              190       200       210       220       230       240

         240       250       260
125-39 ISRLLKHNPSQRPMLREVLEHPWITANSSKPS
       ::::::::::::::::::::::::::::::::
24-295 ISRLLKHNPSQRPMLREVLEHPWITANSSKPS
              250       260       270
```